[5]Claims 186 and 187 are unclear as to what is meant by the limitations therein. In claim 186, first portions of bridging entities seem to inherently be detectable at least via their chemical structure. Given this inherent detectability, how can it not contain a signal-generating portion? Similarly, how can the second portion be cited in claim 187 not contain a signal-generating portion as also discussed via its structure? Also, how can claim 187 be practiced given its ultimate dependence from claim 154 which requires a signal-generating portion in the second portion of the bridging entity indirectly via its binding to a signalling entity? Clarification of what is meant by these claim limitations is requested.

[6]Claims 199 and 200 are confusing in that "nonradioactive" is cited in claim 199 whereas a "radioactive moiety" is cited in claim 200. What is meant to be radioactive versus non-radioactive? Clarification is requested.

[7]Claims 206-208 indicate a soluble phase or immobilization but do not define what step of the claimed methods that these pertain to. Is immobilization of the analyte which results in an immobilized complex at the end of the method or alternatively is the bridging or signalling entity immobilized separately or before complex formation? Clarification is requested.

[8]The kit claims such as claim 209, last two lines, contain the phrase "which molecular bridging entity and signalling entity form . . ." which is vague and indefinite as to whether the kit contents are limited to having formed a detectable complex. The wording of the kit claims are unclear as to what complexes may or may not be already formed within the scope of the claims.

The indefiniteness rejection is respectfully traversed.

The remarks which follow below are directed to the eight points bracketed in bold above.

[1] The "direct" and "indirect" detection issue has been thoroughly addressed above (see this Amendment, page 35, first full paragraph). Those remarks are incorporated by reference for application to the instant method and kit claims (261-282).

[2] The issue of the term "low" as applied to the nucleic acid sequence of repeating low complexity has likewise been thoroughly addressed above (see this Amendment, page 35, last paragraph, through page 36, first two lines). Those remarks are incorporated by reference for application to the method and kit claims above.

With respect to the term "low" as it is applied to the "molecular weight organic compound" recited in new dependent claim 157 and 209 it is submitted that this usage passes the statutory strictures for indefiniteness. Although the phrase "low molecular weight organic compound" could be taken as relative in the abstract, it is nevertheless believed that the expression takes on a sufficiently precise meaning when a person of ordinary skill in the art reads it together with the details contained in the specification. Moreover, the actual and precise molecular weight of the organic compound is not critical to the practice of the instant invention. Consideration to the foregoing remarks is respectfully urged.

[3] The "variant" issue has also been addressed by Applicants' remarks above (see this Amendment, page 36, first full paragraph), which are incorporated by reference here for the new method and kit claims.

[4] Regarding the citation of "modified" and "naturally occurring" both in claim 195 (now new claims 187 and 239 above), Applicants contend that such language is proper and definite under the statute. Similar language ("naturally occurring modified DNA") appeared in the original claims (see originally filed claim 39). Further, Applicants must point out that the disclosure describes such an embodiment on page 21, second paragraph. There, Applicants disclose:

> In addition, the signal generating portion of the signalling entity need not be a polynucleotide which has been chemically modified or artificially altered in any way. Some biological systems perform in vivo modifications which can be utilized by this system. One such system is the phage T4 grown in E. coli. T4 DNA has a very high content of glycosylated C residues. It is possible to insert (clone) a low complexity repeating polynucleotide sequence into phage T4. This phage would then be naturally propagated and glycosylated in the host. The viral DNA can be isolated from E. coli and bound to a complementary sequence on the bridging moiety. Detection could then be accomplished via a lectin/enzyme system, or lectin/fluorescent dye, or lectin/electron dense material, or lectin/radioactive label, using the natural glucose residues on the T4 DNA as points of anchorage. Other T (even) phages such as T2, T6, or T8 can also be used.

Thus, the meaning of "a naturally occurring modified oligo- or polynucleotide" in claims 187 and 239 is clarified by the instant disclosure itself. Notwithstanding the disclosure, the expression "naturally occurring oligo- or polynucleotide" has attained an art-recognized meaning. See, for example, claim 4 in U.S. Patent No.

4,987,065 (copy attached as Exhibit 5) which claim recites "a naturally occurring highly modified nucleotide."

[5] The subject matter of former claims 186 and 187 has not been retained in the new claims above. Accordingly, any rejection has been rendered moot.

[6] The issue of "non-radioactive" with respect to former claims 199 and 200 is believed to have been addressed by the new claims presented above, which include both radioactive and non-radioactive signalling and signal detection. The new claims conform to proper Markush groups. See footnote 1 above, page 32.

[7] With respect to former claims 206 and 208 (now replaced by new claims 271 and 273) it is noted first that the latter claim calls for a method "wherein the molecular bridging entity or the analyte of said detectable complex is immobilized." Formerly in claim 208, the signalling entity was recited in the alternative as being immobilized. In the first paragraph on page 28, there is given a description of immobilization with reference to Wahl et al., U.S. Patent No. 4,302,204 for information on immobilization involving a nucleic acid segment. Given the instant disclosure and the level of skill in the art (as exemplified by the Wahl patent), Applicants respectfully contend that such immobilization can be effectively practiced, without undue experimentation, before or even after complex formation.

[8] In presenting the new kit claims above, Applicants have purposely deleted the offensive phrase "which molecular bridging entity and signalling entity form . . ." See new claims independent kit claim 275. Reconsideration of this former ground of rejection is respectfully urged.

It is believed that the presentation of the new method and kit claims satisfactorily overcome all of the previous indefiniteness grounds set forth in the January 10, 1995 Office Action.

F. <u>The Rejection Under 35 U.S.C. §103</u>

Former claims 154, 155, 157-163, 171-225, 227-229, 231, and 233-238 stand rejected under 35 U.S.C. §103 as being unpatentable over Dunn's 1977 <u>Cell</u>

publication, *supra,* taken in view of Ward et al., U.S. Patent No. 4,711,955. The Examiner's considerable and detailed comments are set forth on pages 8-20 of the January 10, 1995 Office Action.

Applicants firmly believe that the obviousness rejection has been thoroughly addressed in the remarks above, beginning on page 39 and continuing through page 43, first full paragraph. Those remarks are incorporated herein. In view of the new claims, their previous remarks to the obviousness rejection and the above submitted exhibits, Applicants respectfully request reconsideration of the art rejection.

G. Correction of Informalities

The two informalities cited by the Examiner at the end of the Office Action have been corrected by the amendments to the specification and the presentation of new claims 150-282.

* * * * * * *

SUMMARY AND CONCLUSIONS

New claims 150-282 are presented above in this continuation application under 37 C.F.R. §1.60. Minor changes to the specification have also been effected above.

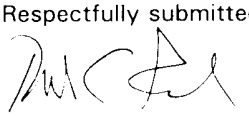
By this Preliminary Amendment, Applicants are attempting to place the instant application in condition for allowance prior to a first examination on the merits. Thus, the issues raised in the May 19, 1995 Office Action (Serial No. 08/342,667) and the January 10, 1995 Office Action (Serial No. 08/032,769) have been addressed by the remarks above and the supporting exhibits (1-11).

The cost for presenting new claims 150-282 is $5,404.00, which cost is based upon 9 independent claims [an excess of 6 X 78 = $468], the first presentation of multiple dependent claims [$250], and a total number of 233 claims [213 claims in excess of twenty X 22 = $4686]. The Patent and Trademark Office is authorized to charge the amount of $5,404.00 to Deposit Account No. 05-1135. If any other fee is due in connection with the claims or this Preliminary Amendment, the cost of such other fee may also be charged to Deposit Account No. 05-1135.

Favorable action on this application and the new claims is earnestly sought.

If it would be helpful to the prosecution of the application, the undersigned may be contacted by telephone during the daytime business hours at (212) 856-0876.

Respectfully submitted



Ronald C. Fedus
Registration No. 32,567
Attorney for Applicants

Enzo Diagnostics, Inc.
c/o Enzo Biochem, Inc.
575 Fifth Avenue (18th Floor)
New York, New York 10017
Telephone: (212) 856-0876
Facsimile: (212) 856-0878